Overview of Lactofen FQPA Risk Assessment for Tolerance Reassessment
June 7, 2001

Introduction

This document summarizes EPA's human health risk findings for the herbicide lactofen, as presented fully in the documents: *Lactofen: Preliminary Human Health Risk Assessment for Tolerance Reassessment,* dated October 12, 2000 and *Revised Drinking Water Exposure Assessment for Lactofen,* dated July 14, 2000. The purpose of this summary is to assist the reader by identifying the key features and findings of the risk assessments in order to better understand the conclusions reached in the assessments. This summary was developed in response to comments and requests from the public which indicated that the risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Lactofen is a member of the diphenyl ether group of herbicides, which includes acifluorfen (lactofen's major metabolite), nitrofen, oxyfluorfen, and fomefasen. In addition, lactofen degrades to acifluorfen in the environment. The Agency has evidence that these compounds induce similar toxic effects but has not yet determined whether these compounds exhibit a common mechanism of toxicity. The Agency defers the cumulative risk assessment of lactofen and the other diphenyl ethers to a later date. For the purposes of tolerance reassessment, EPA is assuming no common mechanism. However, EPA is conducting an aggregate assessment for lactofen and sodium acifluorfen because acifluorfen is an environmental degradate of lactofen. To date, EPA has only identified two classes of chemicals that share a common mechanism of action and are being considered together for purposes of a cumulative assessment (e.g., the organophosphates and some carbamates.) In addition, EPA is in the process of developing methodology to conduct a cumulative assessment.

Because lactofen is under review for tolerance reassessment only, no occupational or ecological risk assessment was conducted. EPA has not reviewed poisoning incidence data for lactofen at this time. This review is limited to food and drinking water, which fall under the purview of FQPA. Occupational and ecological risks fall under the purview of FIFRA. There are no residential uses of lactofen.

The risk assessments for lactofen are available on the Internet and in the Pesticide Docket for

public viewing. Meetings with stakeholders (i.e., growers, environmental groups, commodity groups, and other government offices) are planned to discuss the identified risks and to solicit input on risk mitigation strategies. This feedback will be used to complete the Tolerance Reassessment Eligibility Decision (TRED) document, which will include the resultant risk management decisions. Before issuing its reregistration decision, EPA plans to conduct a closure conference call with interested stakeholders to describe the regulatory decisions presented in the RED.

Use Profile

Broad Spectrum Herbicide registered for use on peanuts, snap beans, soybeans, cotton, and fruiting vegetables for both pre- and post-emergent control of weeds. Lactofen is not registered for residential use.

Formulations: Lactofen is sold in the United States under the trade names Cobra® and Stellar®. Lactofen is formulated as technical grade (71.7% active ingredient), manufacturing use product (60% active ingredient), and emulsifiable concentrate (23.2 to 26.6% active ingredient).

Methods of Application: Aerial and ground application; band treatment, broadcast, directed spray, low volume spray, soil broadcast treatment, and soil incorporation.

Use Rates: Lactofen is generally applied at a rate of 1 lb ai or less per application with a total application of 1 lb ai/A per year.

Annual Poundage: Approximately 235,000 pounds of lactofen active ingredient are applied annually to nearly 2.2 million acres. Lactofen's largest markets in terms of total pounds of active ingredient are soybeans (85%) and cotton (12%). The remaining use is primarily on dry and fresh beans and peas.

Percent Crop Treated: Sites on which lactofen has the highest percent of crop treated include soybeans (3%) and cotton (2%).

Registrant: Valent USA

Human Toxicity

- Lactofen has low acute toxicity via the oral, dermal, and inhalation routes of exposure; causes mild skin irritation; and is not a dermal sensitizer. The manufacturing use product (60% ai) is a moderate eye irritant.

- Lactofen has been placed in Acute Toxicity Category IV for acute oral and inhalation toxicity

and Category III for acute dermal toxicity.

Human Health Risk Assessment

Acute Dietary (Food) Risk

Acute dietary risk is calculated considering what is eaten in one day. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day and no adverse health effects would be expected) does not exceed the Agency's level of concern. The aPAD is the reference dose (RfD) adjusted for the FQPA Safety Factor.

An acute dietary analysis was conducted, which utilized average residue values from field trial studies, concentration factors from processing studies, and percent crop treated information. The dietary risk assessment was based only on residues of lactofen because metabolites, such as acifluorfen, are not expected to be present at significant levels. Because no relevant effects following a single exposure of lactofen were identified for the U.S. general population, an acute dietary risk assessment for the entire U.S. population was not conducted. However, an assessment was conducted for the population subgroup of "females 13+ years old" because developmental effects were noted in one rat developmental toxicity study. These effects are believed to be relevant to women of child bearing age.

The acute dietary exposure analysis is a Tier 2 assessment based on the Dietary Exposure Evaluation Model (DEEM™). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

- The acute dietary (food) risk estimate is not of concern. Acute dietary exposure to lactofen comprises < 0.1% of the aPAD.

- A NOAEL of 50 mg/kg/day was established for "females 13+ years" based on decreased fetal weight and skeletal abnormalities in a rat developmental toxicity study. Both the decreased fetal weight and the skeletal abnormalities are presumed to occur after a single exposure (dose), and thus, are appropriate for this acute risk assessment.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and intra-species variation (10X).

- A 3X FQPA safety factor was retained for acute dietary exposures for females 13+ based on the following:

  < no increased susceptibility from *in utero* and/or postnatal exposure to lactofen in rats,

< adequate data to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment, and

< a data gap for a rabbit developmental toxicity study.

- The acute PAD for females 13+ is 0.17 mg/kg/day. No acute PAD has been established for the general population.

Chronic Dietary (Food) Risk

For the chronic (non-cancer) dietary risk assessment, an average of consumption values for each population subgroup is combined with average residue values in/on commodities over a 70-year lifetime to determine average exposure. A risk estimate that is less than 100% of the chronic PAD (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) does not exceed the Agency's level of concern. The chronic dietary analysis utilized anticipated residue values based on field trial studies, concentration factors from processing studies, and percent crop treated information.

- The chronic dietary (food) risk estimate is not of concern. Dietary exposure to lactofen constitutes <0.1% of the chronic PAD for the U.S. population and all subpopulations.

- The NOAEL used in the chronic dietary assessment is 0.79 mg/kg/day, based on kidney lesions and weight changes to the thyroid and adrenal glands, and is derived from a chronic oral toxicity study in dogs.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and variation (10X).

- The FQPA Safety Factor is 1X for chronic dietary exposures because the data gap for a developmental toxicity study in rabbits and has no bearing on chronic exposure. This study would only provide information relevant to *in utero* exposures.

- The chronic PAD is 0.008 mg/kg/day for all population subgroups.

Cancer Dietary (Food) Risk

Chronic (cancer) dietary risk is also calculated by using the average consumption values for food and average residue values for those foods over a 70-year lifetime. The chronic exposure value is combined with a linear low-dose (Q_1*) approach to determine the lifetime (cancer) risk estimate. The Agency generally considers risks greater than 1×10^{-6} (1 in 1 million) to exceed its level of concern for cancer dietary exposure.

- Lactofen is classified as a B2 chemical carcinogen (probable human carcinogen), based on the appearance of liver tumors (adenomas and carcinomas) in mice and liver lesions such as neoplastic nodules and foci of cellular alteration (possible tumor precursors) in rats.

- A linear low-dose (Q_1*) approach was used to characterize human health risk. The unit risk, or Q_1*, is based on increased incidence in liver tumors in mice and liver lesions in rats. The Q_1* is 1.19×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents using the 3/4 scaling factor.

- The results of this analysis show that the cancer dietary risk from food alone is 8×10^{-8} for the general U.S. population, which is below the Agency's level of concern.

- The registrant has voluntarily submitted several toxicity studies on lactofen's mechanism of action. The Registrant contends that lactofen is carcinogenic by a threshold mechanism for carcinogenicity based on peroxisome proliferation. The Registrant has also requested that EPA re-evaluate the approach to cancer risk assessment for lactofen and use a nonlinear margin of exposure (MOE) approach.

- In 1996 and 1999, EPA proposed new cancer risk assessment guidelines which stated that nonmutagenic carcinogens known to cause cancer via a threshold mechanism could be assessed using a nonlinear MOE approach rather than the Q_1* method.

- EPA has recently reviewed the new studies and determined that lactofen acts via a peroxisome proliferation mechanism. As a result of the evaluation of the recently submitted mechanistic data, the Agency is currently reevaluating its approach to the quantification of the cancer risk for lactofen.

Fate and Transport

- Lactofen degrades very quickly in the environment, with some studies suggesting a half-life of three days. The primary degradate is acifluorfen, which is also registered for use as an herbicide in agricultural and residential settings. A minor degradate is des-ethyl lactofen.

- Environmental fate data suggest that while lactofen is not likely to reach water resources in any significant quantities; acifluorfen is both persistent and mobile in the environment.

- Acifluorfen has been found in monitoring studies of ground and surface water, but insufficient monitoring data are available to quantify the risk from lactofen and acifluorfen in drinking water.

Drinking Water Dietary Risk

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses

either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution from water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food and then calculates a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring estimated environmental concentration (EEC) levels exceed this level. EECs that are above the corresponding DWLOC exceed the Agency's level of concern. Modeling is generally considered to be an unrefined assessment that provides high-end estimates.

- **Acute drinking water concentrations** for surface water (modeled with GENEEC) and groundwater (modeled with SCI-GROW) were less than the acute DWLOCs of 5100 ppb for females age 13+; therefore, acute dietary risk from food and drinking water are not of concern. The acute surface water EEC for lactofen is 0.62 ppb, and the acute groundwater EEC is 0.006 ppb.

- **Chronic drinking water concentrations** for surface water and groundwater were less than the chronic DWLOCs of 280 ppb for the U.S. population and 80 ppb for children age 1-6; therefore, chronic dietary risk from food and drinking water are not of concern. **Chronic drinking water concentrations** for surface water and groundwater were also less than the cancer DWLOC of 0.3 ppb. The average chronic surface water EEC for lactofen is 0.022 ppb and the chronic groundwater EEC is 0.006 ppb.

- However, **the chronic drinking water concentration** of acifluorfen (from lactofen) exceeds the cancer DWLOC of 0.7 ppb for acifluorfen. The average chronic ground water EEC for acifluorfen (from lactofen) is 10.3 ppb; the average surface water EEC is 0.34.

- The Agency has a potential cancer risk concern for acifluorfen derived from lactofen in groundwater. A small-scale prospective groundwater study is required to address this concern. The lactofen registrant is currently conducting such a study in Michigan, and sampling is scheduled to continue until June, 2001. Interim reports have been submitted and are under EPA review; the final study report is scheduled to be submitted by the end of 2001.

Residential Risk

Lactofen is not registered for residential uses; therefore the Agency did not assess residential risk.

Aggregate Risk

Aggregate risk looks at the combined risk from exposure through food, drinking water, and, if appropriate, residential uses. Generally, all risks from these exposures must be less than 100% of the aPAD and cPAD (*non-cancer*) and the aggregate cancer risk must be less than 1×10^{-6}. For lactofen, the aggregate risks would include food and drinking water exposure from both lactofen (parent) and

sodium acifluorfen (degradate) .

- **The Agency has no concern for the aggregate exposure to lactofen *per se*. However, EPA does have a concern for cancer risk from acifluorfen in water resulting from lactofen applications to crops and subsequent degradation to acifluorfen in the environment.** The aggregate risk from acifluorfen is discussed in the overview and preliminary risk assessment documents for sodium acifluorfen.

Occupational and Ecological Risk

As stated previously, no occupational or ecological risk assessment was conducted for lactofen. This review is limited to food and drinking water, which fall under the purview of FQPA. Occupational and ecological risks, which fall under the purview of FIFRA, are not required for tolerance reassessment.

Potential Alternatives

As part of the tolerance reassessment process, EPA has conducted a preliminary analysis of potential alternatives to lactofen. These alternatives are summarized in the table below. EPA is seeking comments on the viability of these alternatives, as well as information on additional alternatives that are not listed below.

REGISTERED ALTERNATIVES FOR LACTOFEN IN SOYBEANS AND COTTON		
Site	Weed	Registered Herbicides Labeled for Weed
Soybeans	Ragweed, common	acifluorfen+fomefasen, chlorimuron+glyphosate, chlorimuron, fomefasen, glufosinate, glyphosate, chlorimuron ethyl+thifensulfuron methyl
	Ragweed, giant	chlorimuron+glyphosate, chloransulam methyl, glufosinate, chlorimuron, glyphosate, chlorimuron ethyl+thifensulfuron methyl
	Waterhemp	acifluorfen+fomefasen, chlorimuron+glyphosate, fomefasen, glufosinate, glyphosate
	Pigweed	acifluorfen+fomefasen, chlorimuron+glyphosate, chlorimuron, fomefasen, glufosinate, thifensulfuron methyl, imazethapyr, imazamox, chlorimuron ethyl+thifensulfuron methyl, glyphosate
	Kochia	imazethapyr, imazamox
	Nightshade	acifluorfen+fomefasen, fomefasen, glufosinate, imazethapyr, imazamox,

REGISTERED ALTERNATIVES FOR LACTOFEN IN SOYBEANS AND COTTON		
Site	Weed	Registered Herbicides Labeled for Weed
	Black nightshade	acifluorfen+fomefasen, fomefasen, glufosinate, imazethapyr, imazamox,
	Mustard	bentazon, bentazon+acifluorfen, acifluorfen+fomefasen, chlorimuron+glyphosate, chlorimuron, fomefasen, glufosinate, thifensulfuron methyl, imazethapyr, imazamox, chlorimuron ethyl+thifensulfuron methyl, flumiclorac pentyl+acifluorfen, glyphosate, chlorimuron ethyl+thifensulfuron methyl
Cotton	Cocklebur, common	oxyfluorfen, DSMA, MSMA, prometryn,+MSMA, diuron+MSMA,, fluometuron+MSMA, glyphosate, bromoxynil
	Croton, tropic	bromoxynil
	Morning glory, annual	oxyfluorfen, diuron+MSMA, bromoxynil, pyrithiobac sodium
	Prickly sida	prometyn+MSMA, DSMA, MSMA, oxyfluorfen+MSMA, glyphosate
	Spurge	glyphosate
	Pigweed	oxyfluorfen, linuron, prometryn,+MSMA, diuron+MSMA, fluometuron+MSMA, glyphosate, pyrithiobac sodium
	Purslane	oxyfluorfen, linuron, glyphosate
	Copperleaf, hophornbeam	oxyfluorfen, linuron, prometryn,+MSMA, diuron+MSMA, fluometuron+MSMA
	Ragweed	oxyfluorfen, glyphosate, bromoxynil
	Jimsonweed	oxyfluorfen, prometryn,+MSMA, diuron+MSMA, fluometuron+MSMA, bromoxynil

Data Needs

The following data gaps have been identified for lactofen:

870.3700 Prenatal Developmental Toxicity Study in Rabbits

860.1850 Confined Rotational Crop Study

Product chemistry studies are required for the 60 and 76% formulations because the composition of these two products has changed as a result of a change in the manufacturing process.

EPA also needs information to clarify the persistence of lactofen in different types of soil and its mobility to groundwater. This information might be provided through new laboratory studies, literature

studies, or unpublished data not previously submitted to EPA.